AMENDMENTS TO THE DRAWINGS

The attached replacement sheets of drawings include changes to Figures 1-3 (attached hereto as **Exhibit 1**). These sheets, which include Figs. 1, 2a-2i and 3, replace the original sheets including Figures 1-3. Annotated sheets showing changes are attached hereto as **Exhibit 2**. The attached replacement sheets of drawings are now labeled with the term "Fig." Additionally, Figs. 2a-2i in the attached replacement sheets of drawings are enlarged and individualized views of the graphs from original Figure 2.

Attachments: Replacement Sheets (**Exhibit 1**) and
Annotated Sheets Showing Changes (**Exhibit 2**)

REMARKS

Claims 1-42 are pending in the subject application. Applicants hereinabove have amended the specification, Figures 1-3 and claims 1, 4-7, 10, 15, 19, 24, 28, 33 and 37. Accordingly, upon entry of this Amendment, claims 1-42 will still be pending and under examination.

Applicants maintain that the amendments to the specification, Figures 1-3 and claims 1, 4-7, 10, 15, 19, 24, 28, 33 and 37 do not raise any issue of new matter, and that these claims, as amended, are fully supported by the specification as originally filed.

In making these amendments, applicants neither concedes the correctness of the Examiner's rejections in the March 20, 2006 Office Action, nor abandons the right to pursue in a continuing application embodiments of the instant invention no longer claimed in this application.

In view of the arguments set forth below, applicants maintain that the grounds of the Examiner's objections and rejections made in the March 20, 2006 Office Action have been overcome, and respectfully request that the Examiner reconsider and withdraw same.

Information Disclosure Statement ("IDS")

Applicants concurrently file an IDS with the U.S. Patent and Trademark Office in connection with the subject application. Acknowledgement of the IDS in the next communication from the U.S. Patent and Trademark Office is respectfully requested.

Objections to Drawings

The Examiner objects to the drawings because (1) "Fig." is to used instead of "Figure" and (2) the graphs in Figure 2 are too small such that the numbers on the x and y-axis are not legible.

In response to the Examiner's above objections to the drawings, but without conceding the correctness thereof, applicants note that Figures 1-3 have been amended. Specifically, applicants have amended the term "Figure" to "Fig." for all drawings. Additionally, the graphs of Figure 2 have been enlarged and are now shown separately as "Figs. 2a -2i".

Thus, applicants maintain that the Examiner's objections to the drawings have been obviated.

Objection to the Specification

The Examiner objects to the specification because pg. 6, "**FIGURES**" should be "**BRIEF DESCRIPTION OF THE DRAWINGS**".

In response, applicants note that the "**FIGURES**" subtitle on pg. 6, line 1 has been amended. Now, the amended subtitle states "**BRIEF DESCRIPTION OF THE DRAWINGS**".

Thus, applicants maintain that the Examiner's objection to the specification has been obviated.

Claim Rejection Under 35 U.S.C. §102(b)

The Examiner states that claims 1-3, 6 and 7 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by WO99/24029 (hereinafter "WO '029"). Specifically, the Examiner states that WO '029 expressly discloses a composition containing arsenic trioxide, water, NaOH and HCl (pg. 27, lns. 20-38).

In response to Examiner's rejection, applicants respectfully traverse.

WO '029 fails to anticipate the claimed invention since it does not teach each and every element set forth in claims 1-3, 6 and 7 for the reasons set forth below.

Independent claim 1 recites a composition for *oral* administration, wherein the composition is prepared by a method comprising (a) adding arsenic trioxide to sterile

water to form a first solution/suspension; (b) adding sodium hydroxide to the first solution to form a second solution/suspension; and (c) adding hydrochloric acid to the second solution to form a third solution.

WO '029 does not disclose an arsenic trioxide composition for *oral* administration. In stark contrast, WO '029 discloses a pharmaceutical composition containing arsenic trioxide which is administered intravenously into a patient. *See, e.g.*, WO '029, pg. 27, lns. 36 to pg. 28, ln. 2; pg. 29, lns. 23-27.

Additionally, WO '029 does not disclose any arsenic trioxide composition for oral administration prepared by a method which involves first adding arsenic trioxide to sterile water to form a first solution/suspension and, secondly, adding sodium hydroxide to said first solution to form a second solution/suspension. Rather, WO '029 teaches that an arsenic trioxide composition for intravenous administration by a method which involves first solubilizing solid ultrapure arsenic trioxide in an aqueous solution of high pH, i.e., a 5M solution of sodium hydroxide, and then adding water to the solubilized arsenic trioxide in 5M sodium hydroxide solution. WO '029, pg. 27, lns. 21-27.

Thus, for these reasons, WO '029 fails to anticipate the claimed invention since it does not teach each and every element set forth in claims 1-3, 6 and 7.

In view of the above remarks, applicants maintain that claims 1-3, 6 and 7, as amended, satisfy the requirements of 35 U.S.C. §102(b), and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §102(a)

The Examiner states that claims 1-3, 7 and 8 are rejected under 35 U.S.C. §102(a) as allegedly anticipated by CN1370540 (Abstract) (hereinafter "CN '540"). Specifically, the Examiner states that CN '540 expressly discloses a composition containing arsenic trioxide, water, NaOH and HCl.

In response to Examiner's rejection, applicants respectfully traverse.

CN '540 fails to anticipate the claimed invention since it does not teach each and every element set forth in claims 1-3, 6 and 7 for the reasons set forth below.

The three sentence abstract of CN '540 does not teach any arsenic trioxide composition for *oral* administration. Furthermore, CN '540 does not teach any arsenic trioxide composition for oral administration prepared by a method which involves first adding arsenic trioxide to sterile water to form a first solution/suspension and, secondly, adding sodium hydroxide to said first solution to form a second solution/suspension. Rather, CN '540 teaches a method which involves dripping NaOH solution to dissolve arsenic trioxide and then using triple distilled water to dilute the solubilized arsenic trioxide in NaOH solution.

Similar to WO '029, CN '540 fails to anticipate the claimed invention since it does not teach each and every element set forth in claims 1-3, 6 and 7.

In view of the above remarks, applicants maintain that claims 1-3, 6 and 7, as amended, satisfy the requirements of 35 U.S.C. §102(a), and request that the Examiner reconsider and withdraw this ground of rejection.

Claim Rejection Under 35 U.S.C. §103(a) - Obviousness

The Examiner states that claims 1-42 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over WO '029 or CN '540. Specifically, the Examiner acknowledges that the prior art does not expressly disclose using specified amounts of arsenic trioxide, water, HCl and NaOH and specific method of preparation. However, the Examiner states that the prior art discloses similar solutions which are used for treatment of leukemia having a neutralized pH and containing NaOH and HCl. The Examiner concludes that it would have been well within the skill in the art to vary the steps and concentrations of NaOH and HCl added so long as the final

solution is at neutralized pH, with the expectation the final solution would be suitable in the treatment of leukemia.

In response to Examiner's above rejection, applicants respectfully traverse, and maintain that the Examiner has failed to establish a *prima facie* case of obviousness against rejected claims 1-42.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed.

The references cited against the rejected claims 1-42 fail to support a *prima facie* case of obviousness since the cited references, whether by itself or combined, do not teach or suggest each element of the rejected claims, and also there would be no reasonable expectation that the claimed invention would succeed.

First, neither WO '029 nor CN '540, or a combination thereof, teach or suggest each and every element of independent claims 1, 10, 19 and 28. As discussed above with the 35 U.S.C. §102(a) and (b) rejections, WO '029 or CN '540 do not teach each and every element of claim 1. To recap, neither of the cited references teach (1) any arsenic trioxide composition for *oral* administration or (2) any arsenic trioxide composition for oral administration prepared by a method which involves first adding arsenic trioxide to sterile water to form a first solution/suspension and, secondly, adding sodium hydroxide to said first solution to form a second solution/suspension.

With respect to claim 10, the cited references do not teach or suggest each and every element of the claim. In addition to the remarks presented immediately above, applicants respectfully point out that, as the Examiner conceded, neither WO '029 or

CN '540 disclose or suggest any of the specified amounts/concentrations of arsenic trioxide, water, HCl and NaOH as recited in claim 10.

WO '029 or CN '540 do not teach or suggest each and every element of the claim 19 for the same reasons mentioned above. Furthermore, applicants note that the Examiner concedes that neither WO '029 and CN '540 expressly disclose the specific method of preparation. Pg. 4, lns. 4-6 of the March 20, 2006 Office Action.

As for claim 28, neither of the cited references teach or suggest any arsenic trioxide composition prepared by a method which involves first adding arsenic trioxide to sterile water to form a first solution/suspension and, secondly, adding sodium hydroxide to said first solution to form a second solution/suspension. Additionally, WO '029 or CN '540, or a combination thereof, do not teach or suggest any of the specified amounts/concentrations of arsenic trioxide, sterile water, sodium hydroxide and HCl recited in claim 28.

With respect to dependent claims 2-9, 11-18, 20-27 and 29-42, none of the cited references teach or suggest any of the elements recited therein.

Thus, the Examiner fails to present a *prima facie* case of obviousness against rejected claims 1-42 since the cited references do not teach or suggest each and every element of claims 1-42.

The Examiner also fails to present a *prima facie* case of obviousness against rejected claims 1-42 since neither WO '029 nor CN '540, or a combination thereof, teaches or suggests that it would have been well within the skill in the art to vary the steps and concentrations of NaOH and HCl added so long as the final solution is at neutralized pH, with the expectation the final solution would be suitable in the treatment of leukemia. None of the references cited give any suggestion, motivation or indication of which parameters are critical or a direction as to which of many possible choices is likely to be successful to one skilled in the art to create the claimed invention recited in claims 1-42.

Additionally, the cited references teach away from the claimed invention. First, neither of the cited references suggest an arsenic trioxide composition for oral administration. Rather, WO '029 endorses an arsenic trioxide composition for *intravenous* administration. Also, neither of the cited references suggest a method of making an arsenic trioxide composition for oral administration by first adding arsenic trioxide to sterile water to form a first solution/suspension and, secondly, adding sodium hydroxide to said first solution to form a second solution/suspension. More specifically, WO '029 endorses a method of making which involves first solubilizing solid ultrapure arsenic trioxide in an aqueous solution of high pH, i.e., a 5M solution of sodium hydroxide, and then adding water to the solubilized arsenic trioxide in 5M sodium hydroxide solution. Meanwhile, CN '540 endorses a method of making which involves dripping NaOH solution to dissolve arsenic trioxide and then using triple distilled water to dilute the solubilized arsenic trioxide in NaOH solution.

The Examiner also fails to present a *prima facie* case of obviousness since there is no reasonable expectation of success. Specifically, the Examiner has not set forth any evidence supporting the notion that one of ordinary skill in the art would reasonably expect that an arsenic trioxide composition for *oral* administration would be safe and consistently predictable in terms of arsenic bioavailability. *See, e.g.*, pg. 24, ln. 6 to pg. 26, ln. 7; pg. 28, lns. 5-20 of the specification; Fig. 1 and Tables 3 and 4 of the specification.

Thus, for the reasons above, the Examiner fails to present a *prima facie* case of obviousness.

Assuming for the sake of argument that WO '029 or CN '540 established a *prima facie* case of obviousness (which applicants vigorous dispute), applicants respectfully maintain that any such *prima facie* rejection would be rebutted by the fact that the claimed invention demonstrates an unexpected advantage, e.g., the claimed

invention has markedly improved cardiac safety profile relative to intravenously-administered arsenic trioxide compositions.

Patients who receive intravenously administrations of an arsenic trioxide composition are more likely to experience dangerous heart complications, such as ventricular tachyarrhythmias. In contrast, patients who receive oral administrations of an arsenic trioxide composition, such as the claimed invention, are significantly less likely to experience such dangerous heart complications. *See* Siu, et al., "Effects of oral arsenic trioxide therapy on QT intervals in patients with acute promyelocytic leukemia: implications on long-term cardiac safety", Blood, 0:2006-01-0054 (March 2, 2006) (hereinafter "Siu et al."), attached hereto as **Exhibit 3.**

Siu et al. teaches that, when measuring for indicators of proarrhythmic risks, a group of sixteen patients who received the claimed invention illustrated the following: significant QTc prolongation greater than 30 milliseconds was only observed at a single-time-point (2 hours post-oral arsenic trioxide composition), QTc prolongation never exceeded 50 milliseconds, and QTc intervals greater than 500 milliseconds was only observed in three patients within four hours of oral arsenic trioxide composition. Importantly, these observations showed virtually no ventricular proarrythmia in all patients studied. More importantly, none of the patients experienced ventricular tachyarrhythmias. These unexpected results are vastly superior to patients who received intravenous arsenic trioxide compositions, where 26% of patients had QT-intervals greater than or equal to 500 milliseconds, with QTc intervals prolonged by 30-60 milliseconds in 36.6% of treatment courses, and by QTc intervals prolonged by more than 60 milliseconds in 35.4% of patients, resulting in ventricular tachyarrhythmias (more specifically, torsades de pointes) in 1% of cases. Siu et al, pg. 10, "Discussion" section.

Therefore, in view of the surprising nature of this invention, one of ordinary skill in the art would not have been able to predict, based on the cited references,

whether the claimed invention would markedly improved cardiac safety profile relative to intravenously administered arsenic trioxide compositions. To maintain otherwise would be hindsight.

In view of the above remarks, applicants maintain that claims 1-42 satisfy the requirements of 35 U.S.C. §103(a) and request that the Examiner reconsider and withdraw this ground of rejection.

Conclusion

In light of all of the foregoing, it is respectfully submitted that this application is now in condition to be allowed and the issuance of a Notice of Allowance is respectfully solicited.

If a telephone conference would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorneys invite the Examiner to telephone them at the number provided below.

Dated: June 20, 2006

Respectfully submitted,

By _____

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I hereby certify that this correspondence is being deposited with the U.S. Postal Service as Express Mail, Airbill No. EV 262736904 US, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date shown below.

Dated: 6/20/06 Signature: _____
Cindy Yang

ANNOTATED SHEET

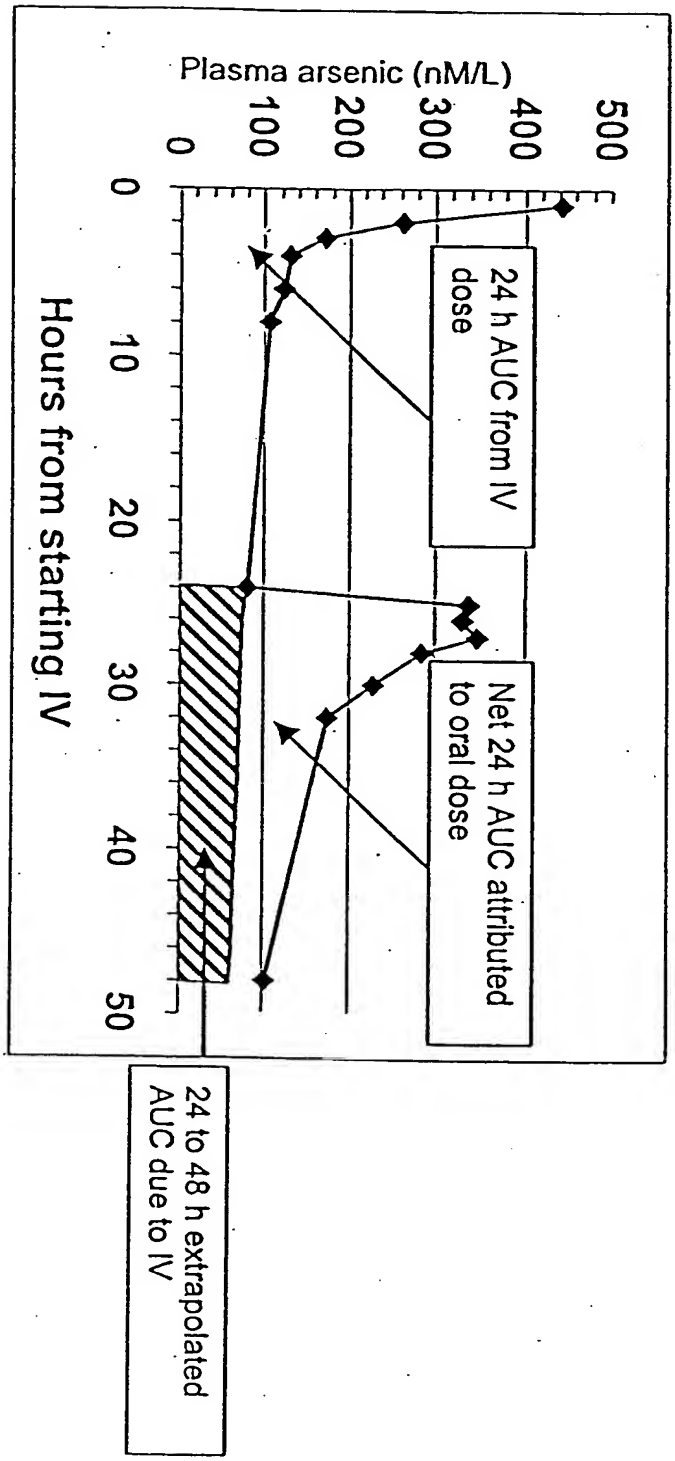

Fig. 1 Figure 1

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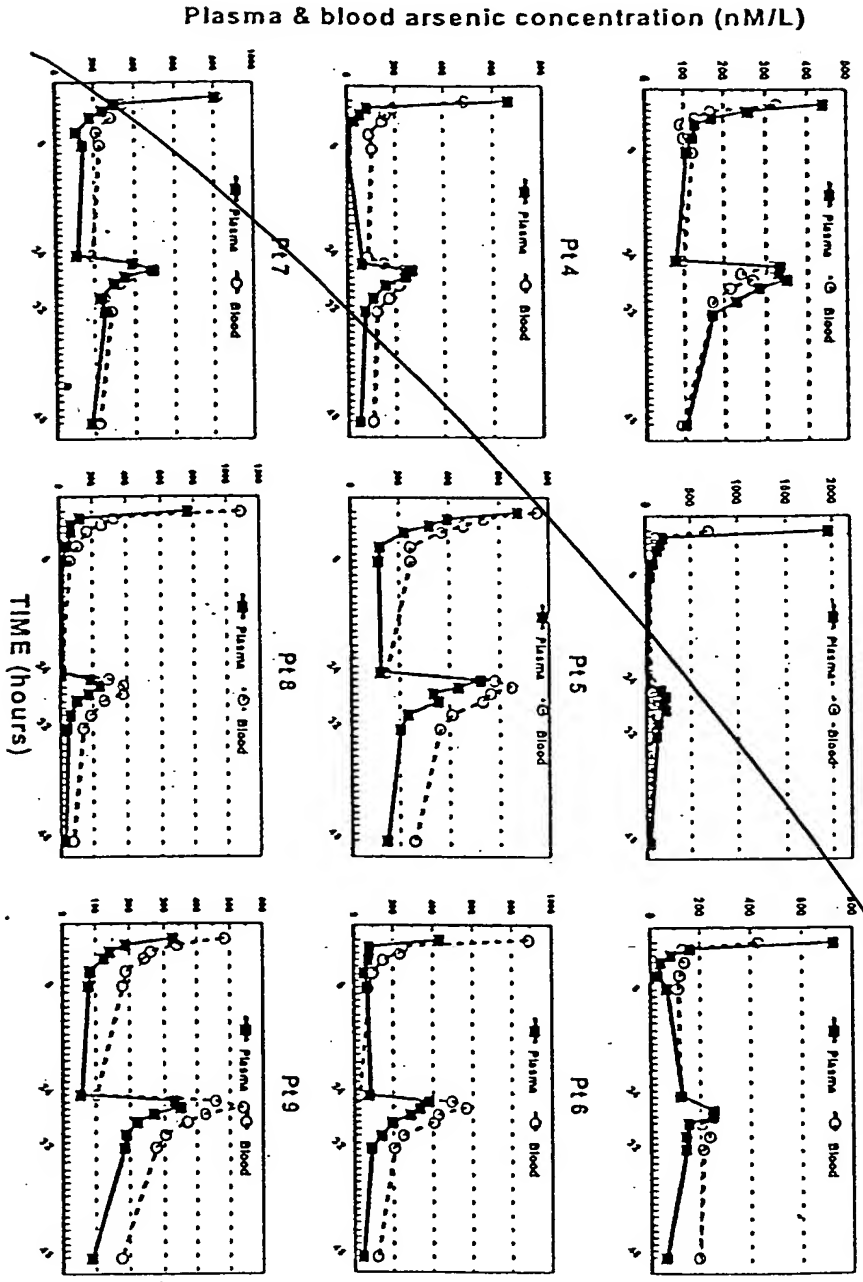

Replaced by New Figs. 2a to 2i.
Figure 2

Fig. 3 Figure 3

Clinicopathologic features and outcome of 12 consecutive patients with relapsed acute promyelocytic leukemia treated with oral As_2O_3

	sex / age	status	previous induction treatment	Time from relapse: last CR	Hb	WBC	Plat	Oral As_2O_3 therapy: duration	additional Rx	result	Consolidation	Latest PCR[1]	DFS	Remarks
1*	M / 23	R1	ATRA + Dauno	11 m	15.6	2.1	87	59 d	Ida	CR	Ida		13 m	
		R2	i.v. As_2O_3 + Ida	10 m	14.0	2.5	25	76 d	ATRA	NR	-	+ (dead)		
2*	M / 33	R2	Dauno / i.v. As_2O_3 + Ida	25 m	13.4	2.1	20	32 d	ATRA	CR	As_2O_3 + ATRA	- (18 m)	19 m +	-
3*	F / 13	R2	ATRA + i.v. As_2O_3	12 m	8.6	1.2	15	30 d	ATRA	CR	As_2O_3 + ATRA	- (18 m)	19 m +	-
4	M / 54	R1	ATRA + Dauno	100 m	8.5	34.8	81	40 d	Ida	CR	Ida	- (18 m)	18 m +	mother: AML
5*	M / 32	R1	ATRA + Dauno + MP	22 m	14.5	2.4	177	33 d	-	CR	Ida	- (18 m)	18 m +	-
6	F / 32	R1	ATRA + Dauno	12 m	12.2	0.8	84	51 d	-	CR	Ida	- (12 m)	18 m +	-
7*	F / 45	R2	ATRA + Dauno / i.v. As_2O_3 + Ida	17 m	11.2	1.9	50	37 d	ATRA	CR	As_2O_3 + ATRA	- (14 m)	17 m +	-
8	F / 65	R1	ATRA	16 m	7.2	2.8	141	28 d	-	CR	As_2O_3 + ATRA	- (12 m)	15 m +	CRF due to DM on CAPD, Ida consolidation omitted due to CRF
9	F / 18	R2	ATRA + Dauno / i.v. As_2O_3 + Ida	12 m	10.1	1.9	180	28 d	ATRA	CR	As_2O_3 + ATRA	- (12 m)	14 m +	-
10*	F / 18	R1	ATRA + Dauno	12 m	8.2	12.6	54	44 d	Ida	CR	Ida	- (6 m)	9 m +	-
11*	M / 45	R1	ATRA + Dauno	240 m	4.2	0.6	9	22 d	-	CR	As_2O_3	- (3 m)	7 m +	Ida consolidation omitted due to high cumulative doses of anthracycline
12	F / 40	R1	ATRA + Ara-c	23 m	8.5	6.5	39	28 d	Ida	CR	Ida	- (3 m)	6 m +	CRHD, double valve rep

*: pharmacokinetic data of oral As_2O_3 have previously been reported[6]
1: PCR for *PML/RARA*, +: positive, -:negative, (time from initial diagnosis)
M: male; F: female, CR: complete remission; NR: non-remission; R1: first relapse; R2: second relapse
CBC: complete blood count; Hb: hemoglobin (g/dL); WBC: white blood cell count (x 10^9/L); Plat: platelet count (x 10^9/L)
m: months; d: days; DFS: disease free survival
ATRA: all-trans retinoic acid; Dauno: daunorubicin; Ida: idarubicin; Ara-c: cytosine arabinoside
CA: carcinoma; AML: acute myeloid leukemia; CRF: chronic renal failure; DM: diabetes mellitus
CAPD: continuous ambulatory peritoneal dialysis; CRHD: chronic rheumatic heart disease; rep: replacement

ANNOTATED SHEET

SHEET 3 OF 5